Methylmalonic acidemia

Description

Methylmalonic acidemia is an inherited disorder in which the body is unable to process certain proteins and fats (lipids) properly. The effects of methylmalonic acidemia, which usually appear in early infancy, vary from mild to life-threatening. Affected infants can experience vomiting, dehydration, weak muscle tone (hypotonia), developmental delay, excessive tiredness (lethargy), an enlarged liver (hepatomegaly), and failure to gain weight and grow at the expected rate (failure to thrive). Long-term complications can include feeding problems, intellectual disability, chronic kidney disease, and inflammation of the pancreas (pancreatitis). Without treatment, this disorder can lead to coma and death in some cases.

Frequency

This condition occurs in an estimated 1 in 50,000 to 100,000 people.

Causes

Mutations in the *MMUT*, *MMAA*, *MMAB*, *MMADHC*, and *MCEE* genes cause methylmalonic acidemia. The long term effects of methylmalonic acidemia depend on which gene is mutated and the severity of the mutation.

About 60 percent of methylmalonic acidemia cases are caused by mutations in the *MMUT* gene. This gene provides instructions for making an enzyme called methylmalonyl CoA mutase. This enzyme works with vitamin B12 (also called cobalamin) to break down several protein building blocks (amino acids), certain lipids, and cholesterol. Mutations in the *MMUT* gene alter the enzyme's structure or reduce the amount of the enzyme, which prevents these molecules from being broken down properly. As a result, a substance called methylmalonyl CoA and other potentially toxic compounds can accumulate in the body's organs and tissues, causing the signs and symptoms of methylmalonic acidemia.

Mutations in the *MMUT* gene that prevent the production of any functional enzyme result in a form of the condition designated mut^0. Mut^0 is the most severe form of methylmalonic acidemia and has the poorest outcome. Mutations that change the structure of methylmalonyl CoA mutase but do not eliminate its activity cause a form of the condition designated mut$^-$. The mut$^-$ form is typically less severe, with more variable

symptoms than the mut^0 form.

Some cases of methylmalonic acidemia are caused by mutations in the *MMAA*, *MMAB*, or *MMADHC* gene. Proteins produced from the *MMAA*, *MMAB*, and *MMADHC* genes are needed for the proper function of methylmalonyl CoA mutase. Mutations that affect proteins produced from these three genes can impair the activity of methylmalonyl CoA mutase, leading to methylmalonic acidemia.

A few other cases of methylmalonic acidemia are caused by mutations in the *MCEE* gene. This gene provides instructions for producing an enzyme called methylmalonyl CoA epimerase. Like methylmalonyl CoA mutase, this enzyme also plays a role in the breakdown of amino acids, certain lipids, and cholesterol. Disruption in the function of methylmalonyl CoA epimerase leads to a mild form of methylmalonic acidemia.

It is likely that mutations in other, unidentified genes also cause methylmalonic acidemia.

Learn more about the genes associated with Methylmalonic acidemia

- MCEE
- MMAA
- MMAB
- MMADHC
- MMUT

Inheritance

This condition is inherited in an autosomal recessive pattern, which means both copies of the *MMUT*, *MMAA*, *MMAB*, *MMADHC*, or *MCEE* gene in each cell have mutations. Most often, the parents of an individual with an autosomal recessive condition are carriers of one copy of the mutated gene but do not show signs and symptoms of the condition.

Other Names for This Condition

- Isolated methylmalonic acidemia
- Methylmalonic aciduria
- MMA

Additional Information & Resources

Genetic Testing Information

- Genetic Testing Registry: Methylmalonic acidemia (https://www.ncbi.nlm.nih.gov/gtr/conditions/C0268583/)

- Genetic Testing Registry: Methylmalonic aciduria due to methylmalonyl-CoA mutase deficiency (https://www.ncbi.nlm.nih.gov/gtr/conditions/C1855114/)
- Genetic Testing Registry: Methylmalonyl-CoA epimerase deficiency (https://www.ncbi.nlm.nih.gov/gtr/conditions/C1855100/)
- Genetic Testing Registry: Vitamin B12-responsive methylmalonic acidemia type cblA (https://www.ncbi.nlm.nih.gov/gtr/conditions/C1855109/)
- Genetic Testing Registry: Vitamin B12-responsive methylmalonic acidemia type cblB (https://www.ncbi.nlm.nih.gov/gtr/conditions/C1855102/)

Genetic and Rare Diseases Information Center

- Methylmalonic acidemia (https://rarediseases.info.nih.gov/diseases/7033/methylmalonic-acidemia)

Patient Support and Advocacy Resources

- Disease InfoSearch (https://www.diseaseinfosearch.org/)
- National Organization for Rare Disorders (NORD) (https://rarediseases.org/)

Research Studies from ClinicalTrials.gov

- ClinicalTrials.gov (https://clinicaltrials.gov/ct2/results?cond=%22methylmalonic+acidemia%22)

Catalog of Genes and Diseases from OMIM

- METHYLMALONIC ACIDURIA AND HOMOCYSTINURIA, cblD TYPE (https://omim.org/entry/277410)
- METHYLMALONIC ACIDURIA DUE TO METHYLMALONYL-CoA MUTASE DEFICIENCY (https://omim.org/entry/251000)
- METHYLMALONIC ACIDURIA, cblA TYPE (https://omim.org/entry/251100)
- METHYLMALONIC ACIDURIA, cblB TYPE (https://omim.org/entry/251110)
- METHYLMALONYL-CoA EPIMERASE DEFICIENCY (https://omim.org/entry/251120)

Scientific Articles on PubMed

- PubMed (https://pubmed.ncbi.nlm.nih.gov/?term=%28Amino+Acid+Metabolism,+Inborn+Errors%5BMAJR%5D%29+AND+%28%28methylmalonic+acidemia%5BTIAB%5D%29+OR+%28methylmalonic+aciduria%5BTIAB%5D%29+OR+%28mma%5BTIAB%5D%29+OR+%28methylmalonicacidemia%5BTIAB%5D%29+OR+%28methylmalonicaciduria%5BTIAB%5D%29%29+AND+english%5Bla%5D+AND+human%5B

mh%5D+AND+%22last+1800+days%22%5Bdp%5D)

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